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*Original article*

# Mammographic changes in postmenopausal women on hormonal replacement therapy

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**Abstract.** The purpose of this study was to investigate the extent of the effects of hormonal replacement therapy (HRT) on the mammographic breast pattern in postmenopausal women. In a hospital-based study mammographic examinations of 81 postmenopausal women were evaluated retrospectively, before and after 1–2 years of treatment with oestrogens or a combination of oestrogens and progestagens. Each individual mammographic film was examined separately, and the glandular tissue was classified according to a modified Wolfe classification. In a screening-centre-based study two consecutive mammograms, with a 2-year interval, of 645 women, of whom 70 were using some kind of hormone therapy, were evaluated retrospectively. In the hospital-based study 31 % of patients treated with combination HRT showed an increase in fibroglandular tissue compared with only 8.7 % in the group treated with oestrogens alone. The difference was statistically significant ($p = 0.046$). In the screening-based study 14.3 % of the women using hormonal therapy showed an increase, whereas in the non-users no increase was found ($p = 1.24 \times 10^{-10}$). After beginning HRT many women (between 14 and 25 % in our experience) can be expected to undergo a mammographically detectable increase in fibroglandular tissue. Radiologists should be aware of the aetiology of such changes, and can obtain information on HRT most conveniently by having the technologist routinely question each patient.

**Key words:** Mammography – Oestrogen – Progestagen – Breast cancer screening – Breast, parenchymal pattern

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## Introduction

In The Netherlands hormonal replacement therapy (HRT) is widely prescribed for postmenopausal women for the treatment of perimenopausal symptoms [1, 2] and prevention of osteoporosis [3, 4]. Furthermore, HRT has been associated with a reduced risk of developing cardiovascular disease [5, 6]. Hysterectomized women are commonly treated with unopposed oestrogens, whereas the addition of a progestagen to the oestrogen is generally accepted in non-hysterectomized women to prevent the development of oestrogen-induced endometrial hyperplasia and carcinoma [7].

There has been a breast cancer screening program in the city of Nijmegen since 1975. Recently, this program was expanded nationwide. All women between the ages of 50 and 70 years are being screened once every 2 years. The women being screened are close to or already in the postmenopausal stage. Normally, the fibroglandular breast tissue decreases, or at least remains stable, in this age group [8–12]. However, occasionally an increase in glandular tissue was noticed at mammography. All these cases concerned postmenopausal women undergoing HRT. This study was therefore undertaken to investigate the frequency of parenchymal breast changes in postmenopausal women receiving HRT.

## Subjects and methods

This study comprised two separate retrospective investigations: a hospital-based study and a screening-centre-based study of the changes in parenchymal breast changes during HRT.

### *Hospital-based study*

*Hormonal replacement therapy.* In this study mammographic examinations of 81 healthy postmenopausal women (mean age ± SD: 54.0 ± 3.3 years) receiving HRT in

**Table 1.** Hospital-based study: distribution of hormone replacement therapy (HRT)

| | Group I[a] ($n = 21$) | Group II[b] ($n = 30$) | Group III[c] ($n = 30$) | Total group ($n = 81$) |
|---|---|---|---|---|
| Oestrogen and progestagen | 21 | 24 | 13 | 58 |
| Oestrogen alone | 0 | 6 | 17 | 23 |

[a] 17$\beta$-oestradiol combined with dydrogesterone
[b] Conjugated oestrogens, either alone or combined with medroxyprogesterone
[c] Conjugated oestrogens, either alone or combined with medrogestone

one of three prospective clinical trials in the gynaecological outpatient department of our university hospital were reviewed. The participating subjects had given their written informed consent after the nature of the study had been fully explained. A total of 21 non-hysterectomized women (mean age ± SD: 54.5 ± 3.3 years) received micronized 17ß-oestradiol (2 mg daily; Zumenon, Solvay-Duphar BV, Weesp, The Netherlands) in combination with dydrogesterone (10 mg daily; Duphaston, Solvay-Duphar BV, Weesp, The Netherlands) during the first 14 days of each 28-day treatment cycle for a period of 2 years [13]. A total of 30 non-hysterectomized women (mean age ± SD: 53.6 ± 3.7 years) received conjugated oestrogens (0.625 mg daily; Premarin, Wyeth-Ayerst Laboratories, Philadelphia, Pa.) either alone or in combination with medroxyprogesterone acetate, 2.5 or 5.0 mg daily continuously, or 5.0 or 10.0 mg daily for the last 14 days of each 28-day treatment cycle for a period of 1 year. A total of 30 hysterectomized women (mean age ± SD: 53.9 ± 3.0 years) received conjugated oestrogens (0.625 mg daily; Premarin, Wyeth-Ayerst Laboratories, Philadelphia, Pa.) either alone or in combination with medrogestone (5 mg daily; Colpro, Wyeth-Ayerst Laboratories, Hoofddorp, The Netherlands), during the last 12 days of each 28-day treatment cycle for a period of 1 year [14]. A combination of oestrogens and progestagens had been prescribed for 58 women (mean age ± SD: 53.4 ± 2.7 years), and the remaining 23 women (mean age ± SD: 54.2 ± 3.5 years) had been treated with oestrogens alone (Table 1).

*Mammography.* Mammography was performed before starting and after either a 1- or 2-year period of HRT as stated above. The patients were otherwise healthy and had no prior breast cancer or major breast surgery. Each individual mammographic film, left and right, before and after HRT,was examined randomly and separately by three radiologists. The 324 mammograms were classified according to a modified Wolfe classification into one of four groups [15]. The Wolfe classification of breast parenchymal patterns was established in 1976. Since that time it has been challenged widely [16, 17], and alternative classifications have been introduced. In order to describe the breast pattern in our populations we modified the Wolfe classification to be re-classified by density alone. This modification did not alter the four original groups outlined by Wolfe, because we used the same percentage boundaries (Fig. 1). An increase in breast density was considered if at least two readings of every mammogram showed a change into a higher group according to the modified Wolfe classification. This method provides more objective proof of a real difference, but may serve to underestimate the actual difference. With a direct comparison of the two mammograms marginal differences of parenchymal density, which would fail to cause a jump from one classification category to the next, would also be recorded.

*Screening-centre-based study*

In an investigation separate from the above-mentioned hospital-based study, 710 consecutive mammographic examinations from our breast cancer screening program were evaluated. The current examination was compared with the previous screening mammography made 2 years earlier, to evaluate changes in fibroglandular densities, correlated with the use of hormonal therapy by these women. A total of 65 women came in for their first screening mammography and were therefore excluded from the study. There were 70 women using some kind of hormonal therapy, either contraceptive or HRT. No data concerning the individual drugs used, their dosage or the duration of therapy was collected. In total, 645 women between the ages of 50 and 70 years were evaluated for changes in the fibroglandular breast tissue according to the modified Wolfe classification.

*Radiographic technique*

All mammograms were obtained by using a high-resolution screen-film combination (Kodak Min-RH Eastman-Kodak, Rochester, N. Y.) and mammography was performed on dedicated mammographic equipment [primarily General Electric CGR Senographe 600T (General Electric Medical Systems Nederland BV, 's Hertogenbosch, The Netherlands), and to a lesser extent, Soredex/Enraf Mamex dcS (Soredex, Orion Corporation, Nilsiankatu, Finland) and Mammomat 3 (Siemens, Erlangen, Germany)]. Mammography consisted of a standard mediolateral oblique (MLO) view and a craniocaudal (CC) view in the hospital-based study. In our breast cancer screening centre the initial screening comprised an MLO as well as a CC view, whereas on subsequent visits the CC view was only added on indication. These indications comprised palpable lesions, mammographically dense breasts, lesions described on the previous mammography and/or changes on the current MLO mammogram as compared with the previous examination.

*Statistical analysis*

For all differences tested on statistical significance we used the Fisher exact test.

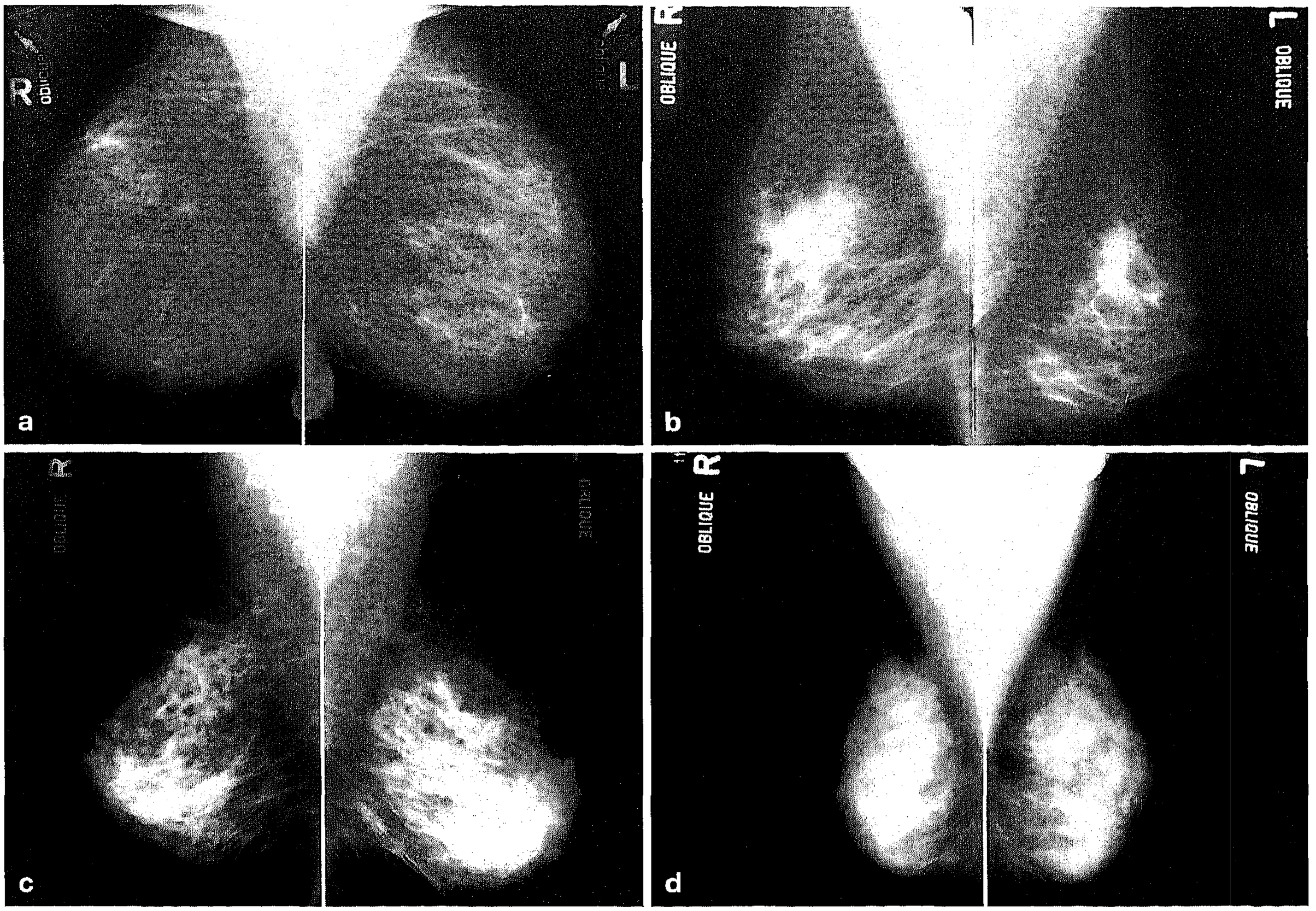



**Fig. 1 a–d.** Classification of breast parenchymal patterns. **a** Parenchyma composed primarily of fat with small areas of increased density; **b** parenchyma mainly fat with densities in the anterior portion of the breast up to a quarter of the breast volume; **c** parenchyma consisting mainly of densities occupying more than a quarter of the breast volume; **d** parenchyma with large areas of increased density which obscures the underlying architecture

## Results

*Hospital-based study*

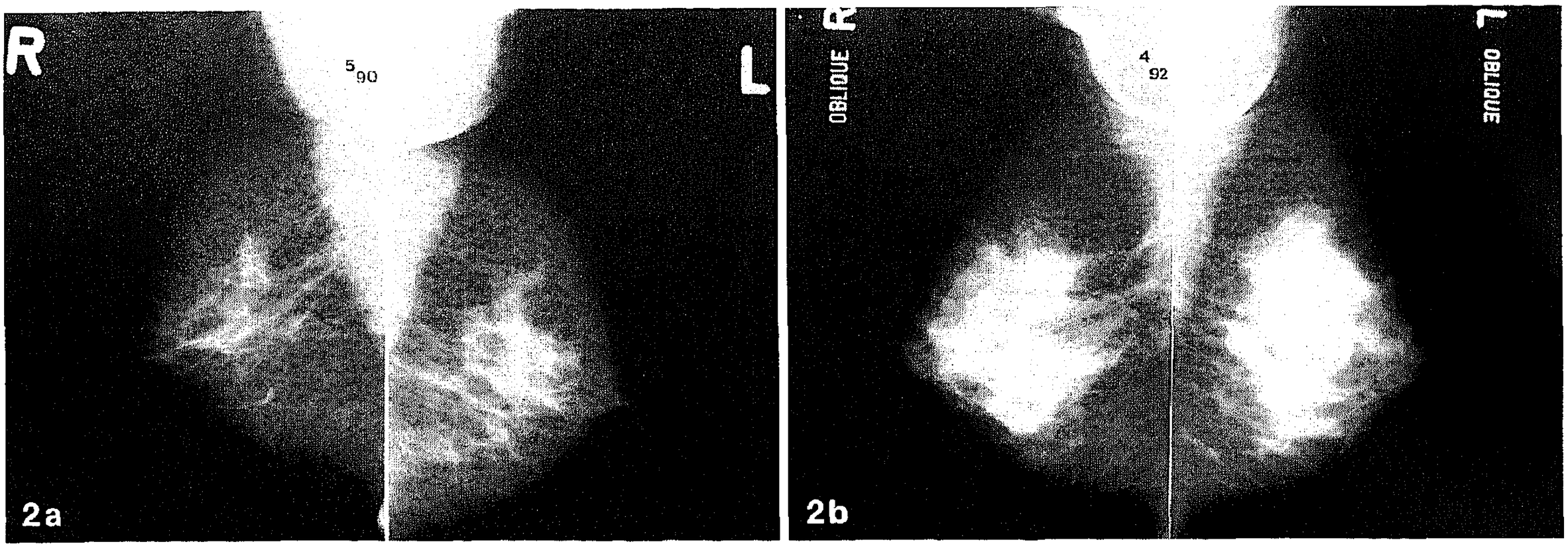
A total of 20 of 81 women (24.7 %) showed an increase in fibroglandular tissue at mammography (Figs. 2, 3). In the group of women receiving a combination of oestrogens and progestagens, 18 of 58 (31 %) showed an increase in glandular density. Of the remaining 23 patients, treated with oestrogens alone, only 2 women (8.7 %) had an increase in glandular breast tissue (Table 2). The Fisher exact test showed a significant difference ($p = 0.046$) between the percentages of women with increased glandular breast density in the oestrogen replacement therapy group and the combined oestrogen/progestagen replacement therapy group. In all 20 cases the increase in fibroglandular tissue was bilateral; no unilateral increase was found in this study.

Of all 81 women in this study, only 4 showed either a unilateral or bilateral decrease in fibroglandular tissue within the intervening interval between the two mammographic examinations; in all other cases the breast densities remained unchanged. In some cases we also noticed an increase in breast volume during HRT. These findings were incidental; no significant trend could be established. Within the group of 20 women showing an increase in fibroglandular breast tissue, no fibroadenomas or cysts could be detected mammographically without the use of ultrasonography, either before or after HRT.

**Table 2.** Hospital-based study: effects of HRT

| | Increase in breast density ($n = 20$) | No change in breast density ($n = 57$) | Decrease in breast density ($n = 4$) | Total group ($n = 81$) |
|---|---|---|---|---|
| Oestrogen and progestagen | 18 (31 %) | 37 | 3 | 58 |
| Oestrogen alone | 2 (8.7 %) | 20 | 1[a] | 23 |

[a] Decrease in breast density in one breast



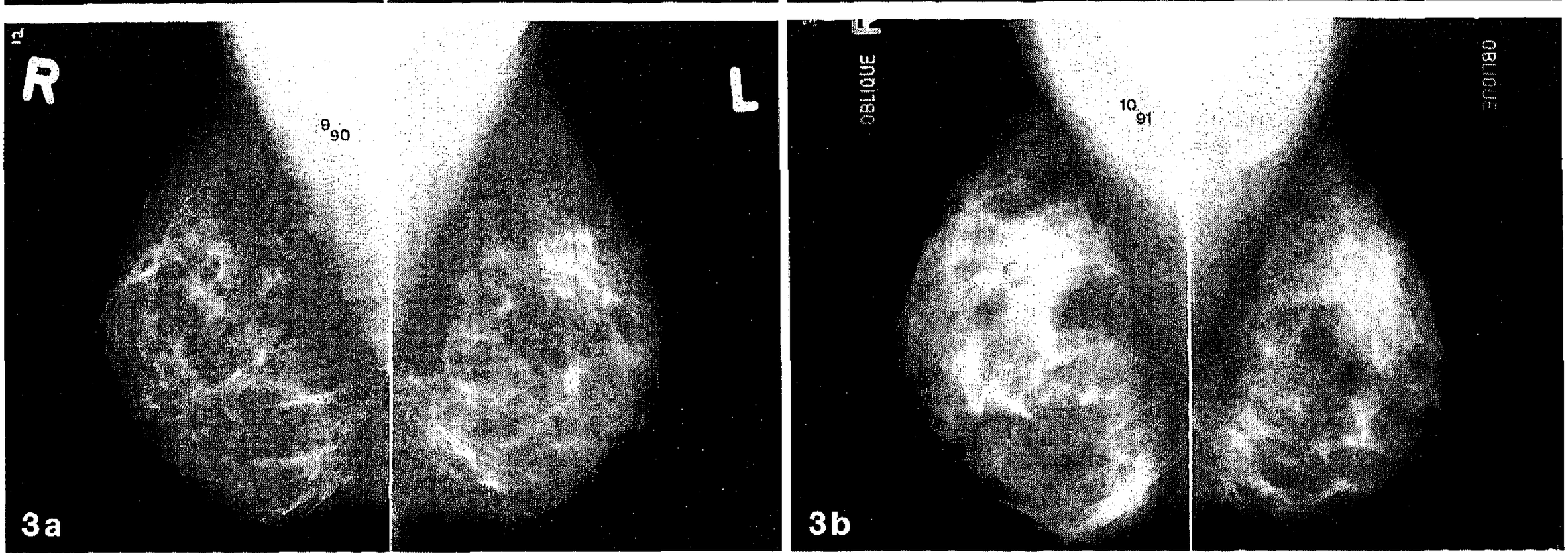




**Fig. 2.** **a** Baseline mammography of a 58-year-old woman, classified into group 2; **b** mammograms obtained after 2 years of hormone replacement therapy (HRT) show a marked increase in fibroglandular tissue (from groups 2 to 3)

**Fig. 3.** **a** Baseline mammography of a 50-year-old woman shows heterogeneous breast parenchyma, classified into group 2; **b** mammograms obtained after 13 months of combined oestrogen/progestagen replacement therapy show diffuse increase in fibroglandular density (from groups 2 to 3)

**Table 3.** Screening center-based study: effects of HRT

| | Increase in breast density ($n = 10$) | No increase in breast density ($n = 635$) | Total group ($n = 645$) |
|---|---|---|---|
| Hormonal therapy | 10 (14.3 %) | 60 | 70 |
| No hormonal therapy | 0 | 575 | 575 |

*Screening-centre-based study*

The breast cancer screening centre-based investigation revealed 10 of 70 women (14.3 %) undergoing hormonal therapy (either contraceptive or postmenopausal), showing an increase in glandular tissue, whereas none of the remaining 575 women without hormonal therapy showed any increase at all. The breast tissue decreased or remained stable in this group (Table 3). The Fisher exact test showed a highly significant difference ($p = 1.24 \times 10^{-10}$) between the group of women using hormonal therapy and the group without hormonal therapy. The majority of the women started with hormonal therapy during the interval between the two mammograms evaluated in this investigation, including all 10 women with an increase in fibroglandular tissue.

## Discussion

In this study we found a considerable percentage of women (24.7 %) using HRT who demonstrated an increase in fibroglandular breast density as demonstrated by repeat mammography. A statistically significant difference between the frequency of mammographic changes in women treated with combined oestrogens and progestagens (31 %) and women treated with oestrogens alone (8.7 %) was found. Although statistically significant, the numbers in the latter group are small and therefore warrant extended research.

In our screening-centre-based study 14.3 % (10 of 70) showed an increase in breast density, compared with 24.7 % (20 of 81) in the hospital-based group. Although the two studies are not fully comparable, the difference in percentages may be clarified by a few points:

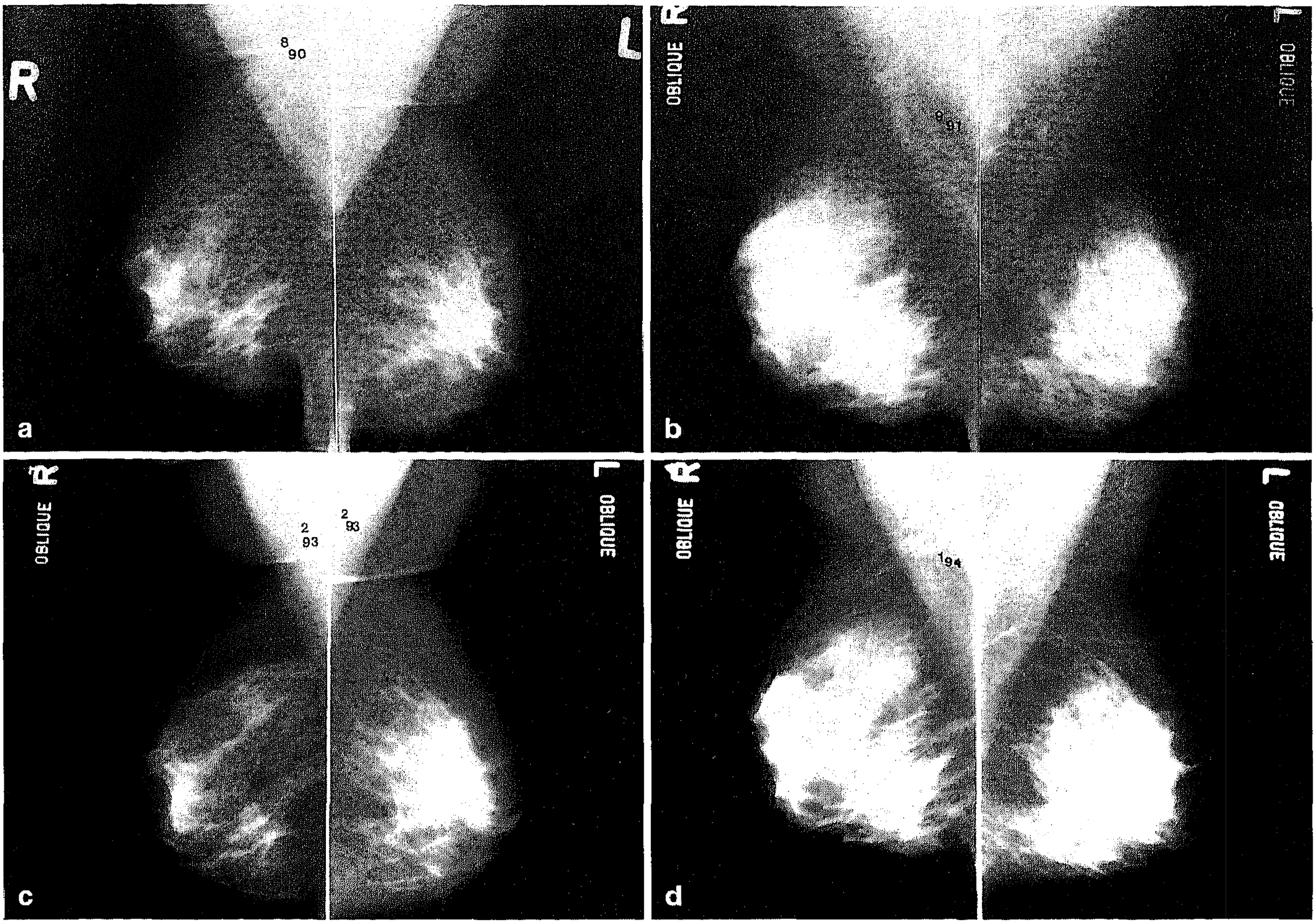



**Fig. 4.** **a** Baseline mammography of a 57-year-old woman, classified into group 2; **b** mammograms obtained after 13 months of oestrogen/progestagen replacement therapy show a marked increase in glandular density from groups 2 to 3; **c** Sixteen months after cessation of HRT, there is a decrease in breast densities back to near-baseline levels; **d** the same patient 11 months after entering another HRT trial, showing a renewed increase in fibroglandular breast tissue

1. Hormonal therapy was not closely monitored in the screening centre-based group, as was the case in the highly motivated hospital-based group of women.
2. The information about hormonal therapy in the screening-based group was based solely on the recollections of the individual women.
3. Within the hormonal therapy group in the screening-based study, contraceptive medication was also included.

In the recent literature there is a retrospective study by Berkowitz et al. [18] comprising a group of 30 women (aged 39–66 years, mean age 55.7 years) receiving HRT, of whom 16 used combined oestrogens/progestagens (mean treatment 17.8 months, range 3–30 months), and 14 received oestrogens alone (mean treatment 27.2 months, range 1–72 months). Five women (17 %), all treated with combined hormonal therapy, showed an increase in fibroglandular tissue in response to HRT. This effect showed a statistically significant difference ($p = 0.045$) from the oestrogen-alone group. In another retrospective study by Stomper et al. [19] 50 postmenopausal women (median age 52 years, range 40–69 years) were treated with either oestrogens alone ($n = 12$) or a combination of oestrogens and progestagens ($n = 38$), for a median period of 18 months (range 6–39 months). Two oestrogen-alone users (17 %) and 10 oestrogen/progestagen users (26 %) showed increased breast densities, but this difference was not statistically significant.

Parts of both above-mentioned studies show similarities with our investigations, e.g. the evaluation of both an oestrogen therapy group and a combination oestrogen/progestagen therapy group [18, 19]; the median age and the median follow-up period of the populations investigated [18, 19]; the percentage of women with an increase in fibroglandular tissue after HRT [19]; and the statistically significant difference between the oestrogen group and the oestrogen/progestagen group [18]. However, there are some differences also. In our hospital-based study we evaluated 81 women, which is approximately two times more than the other two studies. Probably therefore we found a statistically significant difference between the frequency of mammographic changes in women treated with combined oestrogens and progestagens and women treated with oestrogens alone. Another difference is that in our study each individual mammographic film, left and right, before and after

HRT, was examined randomly and separately and classified according to a modified Wolfe classification into one of four groups by three radiologists. In both abovementioned studies [18, 19] this systematically blinded procedure was not used; instead, all mammographic examinations of the individual women before and after HRT were analysed simultaneously.

The statistically significant difference between the women being treated with oestrogen alone and those treated with a combination of oestrogen and progestagen is consistent with other published investigations [18–20]. It is suggested that in addition to the effects of oestrogens on breast tissue, progestagens have an ambiguous influence on the mammary duct epithelium. Besides a known antagonistic response, progestagens act in synergism with oestrogens especially on the distal portion of the ducts [21]. Furthermore, Key and Pike [22] described that the mitotic rate of breast cells is higher during the luteal phase of the menstrual cycle than during the follicular phase, which could be interpreted to suggest a progestagen influence. These two observations may contribute to the explanation of the significant difference between the oestrogen-alone group and the combined oestrogen/progestagen group found in our study.

In those women investigated some time after cessation of HRT we found a decrease in mammographic tissue density almost to the levels prior to HRT. This is in accordance with other studies [18–20]. In a couple of our cases there was a renewed prescription for replacement therapy, which resulted in an immediate increase in glandular density (Fig. 4). This again strongly indicates a causal relationship between an increase in fibroglandular breast tissue and HRT.

Numerous epidemiological studies on the risk of breast cancer for postmenopausal women after treatment with HRT, either oestrogens alone or a combination of oestrogens and progestagens, have been conducted [22–28]. The results of these studies are contradictory. There are studies showing no increased risk after HRT [23, 24], whereas other investigations suggest a slightly increased risk of breast cancer [22, 25, 26]. There is a growing consensus that there is a tendency for the risk to increase with increasing duration of treatment. Bergkvist et al. [26] found a relative risk of 1.7 in women with more than 9 years of HRT use. Hypothetically, the possibility exists that the relatively increased risk of breast cancer after prolonged use of HRT will affect primarily those women showing increased fibroglandular breast tissue at mammography after HRT. This of course can only be verified in an additional extensive and carefully set up investigation with a long-term follow-up.

After beginning HRT, many women (between 14 and 25 % in our experience) can be expected to undergo a mammographically detectable increase in fibroglandular tissue. This contradicts the more common situation in which glandular density in non-treated women decreases or remains stable after menopause. Radiologists should be aware of the aetiology of such changes, which may hamper the detection of malignant lesions and can obtain information on HRT most conveniently by having the technologist routinely question each patient. Special attention should be given to these mammographic examinations for signs of incidental malignancy such as solid masses, architectural distortion, microcalcifications and/or skin changes. These women should be followed carefully, as the incidence of breast cancer increases with age. Early and small carcinomas may not be detected as early as would be the case in women without HRT. Therefore, a more frequent (yearly) screening of these women should be considered in each case [29].

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